UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

Date: October 29, 1998

MEMORANDUM

Subject: EPA Reg. No: 007173-EU DIFETHIALONE 0.5% DRY CONCENTRATE
DP Barcode: D249635
Case No: 062390

From: Dennis McClain, Biologist
Technical Review Branch
Registration Division (7505C)

To: Peg Perreault
Insecticide-Rodenticide Branch
Registration Division (7505C)

Applicant: LiphaTech
3600 West Elm Street
Milwaukee, WI 53209

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt
3-(3-(4'-bromo(1,1'-biphenyl)-4-yl) -1,2,3,4- tetrahydro-1-naphthyenyl)-4-hydroxy -2H-1-benzothiopyran-2-one	0.5
Inert Ingredient(s):	99.5
Total:	100.0%

ACTION REQUESTED: LiphaTech has submitted the following acute tox data to support their application for registration of a new difethialone product. In addition, they are asking for a waiver of the requirement for an acute inhalation study.

BACKGROUND: LiphaTech Inc.has submitted five (5) tox studies: acute oral LD50, acute dermal LD50, eye irritation, dermal irritation, and skin sensitization with MRID numbers 446494-01 and 446473-02 thru 05 respectively.

RECOMMENDATIONS:

The five submitted studies have been reviewed and found to be acceptable.

The acute toxicity profile for EPA Reg. No. 007173- EEU is as follows:

acute oral toxicity	II	Acceptable
acute dermal toxicity	III	Acceptable
acute inhalation toxicity	Waiver request	
primary eye irritation	III	Acceptable
primary skin irritation	IV	Acceptable
dermal sensitization	No	Acceptable

With respect to the waiver request for acute inhalation toxicity, the registrant has stated "Several attempts have been made by LiphaTech Inc. to conduct an inhalation study on this material. In all attempts, the physical characteristics of the product caused it to adhere to the nasal passages of the test animals. We were unable to develop a scientific design that would allow the product to be delivered to the lungs of the test animals. Based on inability to dose the test animals, we are requesting a waiver of this data requirement."

TRB has not received sufficient information to reach a conclusion on this waiver request. The registrant has indicated that several attempts have been made to conduct an inhalation study on this material; we should have additional information regarding the attempts to mill this product or to otherwise reduce the particle size. In addition, we should have information (preferably the CSF) regarding the complete composition of this formulated product.

LABELING:

The following is tentative precautionary labeling, based on the five submitted studies, and as obtained from the Labeling Review System:

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Date: 10/29/98 LABEL REVIEW SYSTEM

ID #: 007173-00224 Liphatech, Inc./Difethialone 0.5% Dry Concentrate

SIGNAL WORD: WARNING

PRECAUTIONARY STATEMENTS:

May be fatal if swallowed. Harmful if absorbed through skin. Causes moderate eye irritation. Avoid contact with eyes, skin or clothing. Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. If person is unconscious, do not give anything by mouth and do not induce vomiting.

OR

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger, or if available by administering syrup of ipecac. If person is unconscious, do not give anything by mouth and do not induce vomiting.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention if symptoms persist.

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

NOTE TO PHYSICIAN:

The proposed label should contain a Note to Physicians. Some suggested types of information include the following:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

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DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

Product Manager: 04
MRID No.: 446494-01

Reviewer: Dennis McClain
Study Completion Date: 5/23/90
Study No.: 89G-0105A

Testing Facility: Toxicon Corporation
Author: Herman S. Lilja

Quality Assurance (40 CFR §160.12): Included p.3

Test Material: Difethialone 0.5% Dry Concentrate; described as an off-white powder
Species: Rats (rattus norvegicus) outbred Sprague Dawley
Age: Approximately 8-12 weeks.
Weight: (fasted) Males 295.6-322.8g Females 235.7 -243.6 For high dose.
Males 235.7-248.5g Females 242.5 -257.5 For middle dose.
Males 288.0-316.4g Females 227.9 -239.2 For low dose.
Source: Charles River Breeding Laboratories (Wilmington, MA)

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: 0.41 g/kg
   Females: 0.41 g/kg
   Combined: 0.41 g/kg
2. **The estimated LD_{50} is** 0.41 g/kg
3. **Tox. Category:** II
4. **Classification:** Acceptable

Procedure (Deviations from 870-1100): None.

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
0.50g/kg	5/5	4/5	9/10
0.45g/kg	4/5	5/5	9/10
0.40g/kg	1/5	2/5	3/10

Observations: (Clinical) 9/10 died in the high dose group (0.5g/kg) between day 3 and day 9. Animals in the middle group died between day 3 and day 8. In the low dose group (0.40 g/kg), 3 animals died between day 6 and day 12.

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"The clinical observations for the high dose group included blood from the ears, dyspnea, lethargy, prostration, lacrimation, piloerection, dry feces, pale eyes, nostril discharge, tachynea, catalepsy, tremors, hyperactivity, somolence, toe walking and watery stool. The observations for the middle dose group included blood from ears, dyspnea, lethargy, dry feces, nostril discharge, piloerection, lacrimation, tremors and tachypnea. The low dose group exhibited blood from ears, dyspnea, lethargy, loose stool, piloerection and tremors.

Gross Necropsy:: In the high dose group, the significant findings were blood in the thoracic cavity, blood clots around the heart, enlarged mandibular lymph nodes, lung hemorrhage, pelvic and abdominal hemorrhage, liver blanched, red lungs, and hemorrhagic bladder.

The middle dose group revealed red and enlarged mandibular lymph nodes, blood in the thoracic cavity, hemorrhage in the lungs, stomach, brain, and abdominal cavity; blanched lungs and liver; and blot clots around the heart.

The low dose group findings were blood in the thoracic cavity, liver and lungs blanched, blood clots around the heart, lymph nodes enlarged, pale kidney and red lungs.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200)

Product Manager: 04
MRID No.: 445773-02

Reviewer: Dennis McClain
Study Completion Date: 1/17/97
Study No.: CHW 60802657

Testing Facility: Corning Hazleton, Inc.
Author: Steven M. Glaza
Quality Assurance (40 CFR §160.12): Included p.4

Test Material: 0.5% Difethialone Dry Concentrate, Lot No. RAT 58 (white powder)
Species: Adult albino rabbbits of the Hra:(NZW) SPF strain
Age: 14-18 weeks old
Weight: Range 2093-2239g
Source: NRP, Inc. Kalamazoo, Michigan

Dermal LD_{50} Testing: >2000mg/kg

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: > 2000 mg/kg 0/5 died at this dose.
   Females: > 2000 mg/kg 0/5 died at this dose.
   Combined: > 2000 mg/kg 0/10 died at this dose.
2. **The estimated LD_{50} is** > 2000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (including deviations from 870.1200): Distilled water was added to the test material "to ensure good contact with the animal's skin." There was 24-hr occluded exposure.

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
100	0/5	0/5	0/10
300	0/5	0/5	0/10
500[a]	0/5	0/5	0/10
500[b]	0/5	0/5	0/10
700	0/5	0/5	0/10
900	0/5	0/5	0/10
2000	0/5	0/5	0/10

[a]Initial dose level
[b]Repeat dose level

Observations: "All animals appeared normal throughout the study" (except for dermal irritation).

The test material produced slight dermal irritation only at the 2000 mg/kg dose level. In this group, 4/5 males were positive for erythema at 1 and 3 days, and one of the four was positive for erythema and desquamation at 7 days. 1/5 males was positive for edema on day 1. 4/5 females showed erythema during the observation period, and 2 of these animals showed slight (grade 1) edema.

Gross Necropsy: There were no visible lesions or observable abnormalities.

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DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400)

Product Manager: 04
MRID No.: 44577303

Reviewer: Dennis McClain
Study Completion Date: 11/5/92
Study No.: 92N1081B

Testing Facility: Bushy Run Research Center (BRRC)
Author(s): R. C. Myers and S. M. Christopher

Quality Assurance (40 CFR § 160.12): Included p.13

Test Material: Difethialone 0.5% Dry Concentrate
Dosage: approximately 80mg (0.1 mL) of the test substance was placed into the conjunctival sac of one eye of each of six rabbits.
Species: New Zealand White Rabbits (3 males & 3 females)
Age: Approximately 12 to 18 weeks old
Weight: 2.0 to 3.5kg
Source: Hazeleton Research Products Inc., Denver, Pa.
Conclusion:

1. **Toxicity Category:** III
2. **Classification**: Acceptable (Moderate irritant)

Procedure Deviations from (870.2400): None

Results: Unwashed eyes

Observations	Number "positive"/number tested				
	Hours				Days
	1	24	48	72	7
Corneal Opacity	0/6	0/6	0/6	0/6	0/6
Iritis	6/6	1/6	0/6	0/6	0/6
Conjunctivae:					
Redness*	6/6	2/6	0/6	0/6	0/6
Chemosis*	0/6	0/6	0/6	0/6	0/6
Discharge*	3/6	0/6	0/6	0/6	0/6

*Score of 2 or more required to be considered "positive."

Summary: There was no corneal involvement; 6/6 animals and 2/6 animals were positive at 1 and 24 hrs respectively for iritis, and 6/6 and 2/6 animals respectively were positive for chemosis. All eyes had completely cleared by seven days.

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DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500)

Product Manager: 04
MRID No.: 44577304

Reviewer: Dennis McClain
Study Completion Date: 11/5/92
Study No.: 92N1081A

Testing Facility: Bushy Run Research Center (BRRC)
Author(s); R C Myers and S M Christopher

Quality Assurance (40 CFR §160.12): Included p.12

Test Material: Difethialone 0.5% dry Concentrate
Dosage: 0.5g
Species: New Zealand White Rabbits (3 males and 3 females)
Age: Approximately 12 to 18 weeks old
Weight: males 2.9 to 3.5kg ; females 2.5 to 3.3kg.
Source: Hazleton Research Products, Inc. (Denver, Pa.)

Conclusion:

1. **Toxicity Category:** IV
2. **Classification**: Acceptable (non-irritant)

Procedure (Deviations from 870-2500): None.

Results: No erythema, edema or other irritation was observed on any of the 6 rabbits through day 7.

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DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)

Product Manager: 04
MRID No.: 445773-05

Reviewer: Dennis McClain
Study Completion Date: 6/22/1990
Study No.: T-9602

Testing Facility: Product Safety Labs
Author: Ralph Shapiro, Ph.D

Quality Assurance (40 CFR §160.12): Included p. 27

Test Material: 0.5% Difethialone, Dry Concentrate, Lot #6598 & PSL Code Number E90413-9; a white powder.
Positive Control Material: 0.08% DNCB in 95% Ethyl Alcohol. Dose Volume 0.4ml.
Species: Hartley Strain albino guinea pigs (males only)
Age: Not reported
Weight: 162-345g
Source: Davidson's Mill Farm South Brunswick, NJ
Method: EPA Guinea Pig Sensitization (Buehler)

Conclusion:

1. **Test material is not a contact sensitizer**.
2. **Classification**: Acceptable

Procedure (Deviations from 870.2600): The dose of 0.07 g was based on preliminary testing in which doses of 0.2 and 0.13 g were found to cause death after several induction applications.

Procedure:
Ten guinea pigs were assigned to the test group; ten to the positive control group (0.08% DNCB dissolved in 95% ethanol). The hair was shorn from each animal on the dorsal thoracolumbar region of each guinea pig. Each animal received a Hilltop dosing chamber and 0.07 g of test material was placed onto each chamber. Hypoallergenic adhesive tape was used to secure each dose chamber. Readings were made at 24 and 48 hrs after induction. This process was repeated on alternate days until a total of nine dose applications had been made. Fourteen days after the ninth application, a challenge dose was applied to naive site on the left side of each guinea pig and to the five naive control guinea pigs. This site was scored for a sensitization response (erythema and edema) at 24 and 48 hrs after challenge. Five guinea pigs from the same shipment were maintained under the same environmental conditions and were treated with the test product at its HNIC at the time of challenge only. These constituted the "naive" group.

Results: Induction Phase- all test animals were negative for erythema; all positive control animals (0.08 % DNCB in 95% alcohol) exhibited varying degrees of erythema at the dose sites throughout the induction phase with occasional eschar and dry flaky skin. Challenge Phase: there were no signs of erythema at 24 or 48 hrs in animals previously induced with the test material, and their naivecontrols were all negative for irritation. Positive control animals: all positive control sites showed erythema at 24 and 48 hrs. During post challenge, erythema was faint and confluent.

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ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D249635
2. **PC CODE:** 128967
3. **CURRENT DATE:** October 29, 1998
4. **TEST MATERIAL:** Difethialone, Dry Concentrate, Lot #E6598

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Toxicon Corp/89G-0105A/5-23-90	446494-01	LD_{50} = 0.41mg/kg	II	A
Acute dermal toxicity/rabbits/ Corning Hazleton Inc./ CHW60802657/1-17-97	445773-02	LD_{50} = >2000mg/kg	III	A
Acute inhalation toxicity		Waiver Request		
Acute eye toxicity/rabbit/Bushy Run Research Center/ 92N1081B/ 11-5-92	445773-03	Moderate irritant	III	A
Acute dermal irritation, rabbit,Bushy Run Research Center;92N1081A/ 11-5-92	445773-04	Non-irritant	IV	A
Acute skin sensitization toxicity/guinea pig/Product Safety Labs/T-9602/6-22-90	445773-05	A non-sensitizer	-	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**